PULMONARY HYPERTENSION: NEW THERAPIES

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OBJECTIVES:
Participants should be better able to:

1. Review current approach to PAH management;
2. Discuss findings re new drugs and approaches;
3. Make recommendations on new pharmacotherapies to treat PH.

THURSDAY, MARCH 3, 2016 9:30 AM
Dr. Hill has received research grants from Actelion, Bayer, Gilead Reata and United Therapeutics and serves as a consultant for Actelion, Bayer and Gilead, but these do not create a conflict related to the following presentation.
Disclosures

Research Grants:
- Actelion, Inc
- Bayer, Inc
-- Gilead, Inc
-- Lung Biotechnology
- Pfizer, Inc
- Reata, Inc
- United Therapeutics, Inc

Advisory Boards
- Actelion
- Bayer, Inc
- Gilead, Inc
- Pfizer, Inc

Lecture Outline

• Brief Update
  – Epidemiology, Definition and Classification
  – Diagnostics – Group 1 v Group 2
• The right ventricle in PAH
• Evidence-based treatment
• Combination therapy
• Ongoing research
Epidemiology and History of PAH

- Prevalence in the U.S.
  - ≈ 50,000 to 100,000 (15,000 to 25,000 diagnosed and treated)
- Circa 1987
  - Due to rapid progression of morbidity and mortality, once patients were diagnosed with pulmonary hypertension they were described as entering “the kingdom of the near-dead”
- 2015
  - Patient survival has dramatically improved as treatment options for PAH have increased


Definition of Pulmonary Hypertension

- General definition
  - Mean PAP ≥ 25 mm Hg at rest, measured by right heart catheterization
- Hemodynamic characterization of PAH
  - Mean PAP ≥ 25 mm Hg, PAWP ≤ 15 mm Hg, elevated PVR (> 3 Wood Units)

Pulmonary Hypertension
World Health Organization Classification

**Group 1**
“PAH”

**Group 2**
PH with Left Heart Disease (PCW > 15)

**Group 3**
PH with Lung Disease and/or Chronic Hypoxia

**Group 4**
Chronic Thromboembolic PH

**Group 5**
Miscellaneous (Sarcoid)

The most numerous subgroup in Group 1 PAH is:

A. Connective tissue disease-related
B. Congenital heart disease
C. Idiopathic
D. Persistent pulmonary hypertension of the newborn
E. Sickle cell disease
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Distribution of Group 1 PAH: REVEAL Registry

N = 2967
- IPAH
- H-PAH
- CTD
- CHD
- Liver disease
- Drug-induced
- HIV
- Other

Pathology of PAH

Overview

• Obstructive lung panvasculopathy
• Prognosis is primarily determined by the functional status of the RV
• Most common cause of death is RV failure


Genetic Mutations in PAH

• BMPR2
  – Major predisposing gene
  – Over 300 mutations have been identified
  – Found in >70% of patients with H-PAH
  – Found in ≈ 20% of patients with IPAH
• ALK-1
  – Major gene when PAH is associated with hereditary hemorrhagic telangiectasia (HHT)
• Less common mutations:
  – Endoglin, SMAD9, Caveolin-1, KCNK3

**Case Presentation**

- 52 year-old man with twenty year hx of PAH assoc with autoimmune hepatitis. Had been stable with excellent exercise capacity (6MWD > 600 m) sildenafil 50 mg tid but now has progressive DOE and fatigue with daily activities (dressing, bathing). Recent leg swelling.
- Denied CP, palpitations, dizziness, syncope
- No HIV risk factors, ↑thyroid, diet pills, illicit drugs, hx thromboembolism
Case Presentation

- T 98.3 BP 110/80 HR 110 RR 20 98% RA
- Neck: Jugular venous pressure of 12 cm, + hepatojugular reflux
- Chest: clear
- Cor: loud P2, RV heave, 3/6 holosystolic murmur at the LLSB, no rubs or gallops
- Extremities: 3+ edema of lower legs

Echocardiography for PAH

Best Screening Tool
- Examine ECHO results for:
  - PA pressure estimate (TR jet² X 4)
  - RV size and function
  - LV size, systolic and diastolic dysfunction
  - Atrial size
  - Valvular heart disease
  - bubble study for intracardiac shunt

Diagnostic Evaluation of Patient

- Echocardiogram:
  - NI LV, RV severely dilated and hypokinetic
  - Severe RA enlargement, Mod-severe TR
  - RVSP 100 mmHg (TR jet $^2$ X 4)
- CXR – increased Rt Descending PA; EKG - RVH
- PFTs: ± restriction, low DLCO, ex desat 86%
- Lung scan low suspicion, neg lower extremity dopplers,
- Hct 32, +ANA; Anti-DNA, TSH, LFTs, HIV all normal,
  BNP 356  6MW distance 312 m

Our Patient
Right Heart Catheterization

<table>
<thead>
<tr>
<th></th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Mean</th>
<th>O2 sat</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td></td>
<td></td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>PA</td>
<td>105</td>
<td>28</td>
<td>54</td>
<td>47%</td>
</tr>
<tr>
<td>Wedge</td>
<td></td>
<td></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>3.4</td>
<td>CI 1.5</td>
<td></td>
<td>PVR 862</td>
</tr>
</tbody>
</table>

- No significant change with inhaled nitric oxide
# Treatment of PAH

**Strategy:**
- Evaluation of disease severity
- Adoption of general measures and supportive therapy
- Assessment of vasoreactivity
- Combination of different drugs and interventions

**Goals of therapy:**
- Improve symptoms, quality of life
- Improve hemodynamics, exercise capacity
- Prevent clinical decline
- Reduce hospitalizations
- Extend survival

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**General Measures and Supportive Therapy**

<table>
<thead>
<tr>
<th>General Measures</th>
<th>Supportive Therapy</th>
<th>Referral to a PAH Clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rehabilitation / exercise</td>
<td>Anticoagulants</td>
<td>Multidisciplinary care</td>
</tr>
<tr>
<td>Psychosocial support</td>
<td>Diuretics</td>
<td>Patient and family education</td>
</tr>
<tr>
<td>Vaccinations</td>
<td>Oxygen</td>
<td>Psychosocial support</td>
</tr>
<tr>
<td>Family planning; Avoid pregnancy</td>
<td>Digoxin</td>
<td>Access to clinical trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Society participation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Support Groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary Hypertension Association</td>
</tr>
</tbody>
</table>

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Current PAH Treatment Algorithm

**RHC with acute vasodilator challenge**

- **Positive response**
  - (>20% to < 40 mm Hg)
  - Trial with oral calcium channel blocker therapy
  - Sustained response
    - Yes (7%)
    - Continue therapy

- **Negative response**
  - Lower Risk (Class II-III)
    - ERAs, PDE5 inhibitors (oral)
    - Iloprost or treprostinil (inhaled)
  - Higher Risk (Class III-IV)
    - Epoprostenol, treprostinil (IV)
    - Treprostinil (s.c)
    - Iloprost or tre (inhaled)
    - ERAs, PDE5 inhibitors (oral)


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**Prognostication: Determinants of Patient Risk**

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Determinants of Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Gradual</td>
<td>Disease progression</td>
<td>Rapid</td>
</tr>
<tr>
<td>II, III</td>
<td>Functional class</td>
<td>III, IV</td>
</tr>
<tr>
<td>Longer (&gt; 400 meters)</td>
<td>6-MWD</td>
<td>Shorter (&lt; 300 meters)</td>
</tr>
<tr>
<td>Peak VO₂ &gt; 10.4 mL/kg/min</td>
<td>CPET</td>
<td>Peak VO₂ &lt; 10.4 mL/kg/min</td>
</tr>
<tr>
<td>Minimally elevated and stable</td>
<td>BNP / NT-proBNP</td>
<td>Significantly elevated</td>
</tr>
<tr>
<td>PaCO₂ &gt; 34 mm Hg</td>
<td>Blood gasses</td>
<td>PaCO₂ &lt; 32 mm Hg</td>
</tr>
<tr>
<td>Minimal RV dysfunction</td>
<td>ECHO cardiography</td>
<td>Pericardial effusion, RV dysfunction, RA enlargement</td>
</tr>
<tr>
<td>RAP &lt; 10 mm Hg; Cl &gt; 2.5 L/min/m²</td>
<td>Pulmonary hemodynamics</td>
<td>RAP &gt; 20 mm Hg; Cl &lt; 2 L/min/m²</td>
</tr>
</tbody>
</table>

• Pharmacotherapies have been approved for what Groups of PH?

A. Group 1 only  
B. Groups 1 and 2  
C. Groups 1, 2 and 3  
D. Groups 1 and 4
Prostacyclin Analogs

<table>
<thead>
<tr>
<th></th>
<th>Epoprostenol</th>
<th>Treprostinil</th>
<th>Iloprost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication / FC</strong></td>
<td>III, IV</td>
<td>III, IV</td>
<td>III, IV</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Continuous IV Inhalation</td>
<td>SC Inhalation</td>
<td>Inhalation</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>20-100 ng/kg/min</td>
<td>Initial = 1.25 ng/kg/min</td>
<td>Usual = 2.5-5 µg, 6-9 times per day</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>2 branded versions available</td>
<td>Inhaled 4 times daily</td>
<td>Administer in well-ventilated areas</td>
</tr>
<tr>
<td></td>
<td>Only PAH clinical study to demonstrate survival benefit</td>
<td>Oral 3 times daily</td>
<td>Max dosage = 45 µg</td>
</tr>
</tbody>
</table>
Subcutaneous Treprostinil

Limitations of SC Treprostinil

- Site pain is major impediment
  - Affects 85%
  - Local measures
  - Topical compounds
  - NSAIDs, narcotics, gabapentin
  - All ± effective
  - Leave in “good” site
Four new PAH drugs have been introduced in the past 2 years. They:

A. Are all oral and in the same class of drug
B. Are all oral and fall into each of the 3 pathways by which previously available drugs work
C. Two are IV and 2 are oral and work by novel pathways
D. Three are oral and one is inhaled and they work by some traditional and some novel pathways
Treprostinil Oral for PAH: FREEDOM-M, C Clinical Trials

- Study design
  - RCTs M – 349 pts for 12 wks
  - C - n = 350 patients on ERA or PDE-5 inhibitor for 16 wks
- Study results
  - High discontinuation rate: 22% of treprostinil-treated patients and 14% of placebo-treated patients
  - Improvement in 6-MWD 23 m in M (p=0.0497) and did not reach statistical significance in C (11m)
  - C result thought to be due to low dose of treprostinil in short-term trial or presence of background therapy


New Oral Prostacyclin Analog Selexipag: GRIPHON Clinical Trial

RCT
- N = 1156
- Selexipag 200 to 800 µg oral twice daily
- Study duration = event driven
- Study endpoint = TTCW
- Results – reduced risk of an adverse clinical event by 39%
  - Reduced hospitalizations
  - No difference in mortality

Sitbon O et al, NEJM 2015 373:2522
# Endothelin Receptor Antagonists

<table>
<thead>
<tr>
<th></th>
<th>Bosentan</th>
<th>Ambrisentan</th>
<th>Macitentan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication / FC</strong></td>
<td>II, III, IV</td>
<td>II, III, IV</td>
<td>II, III, IV</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>62.5 mg twice daily for 4 weeks then 125 mg twice daily</td>
<td>5 mg and 10 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td>Sustained receptor binding and enhanced tissue penetration</td>
<td></td>
</tr>
</tbody>
</table>

## Macitentan for PAH: SERAPHIN Clinical Trial

*P < 0.05

<table>
<thead>
<tr>
<th></th>
<th>Macitentan 10 mg (N = 242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average duration of treatment (event driven)¹</td>
<td>103.9 weeks</td>
</tr>
<tr>
<td>Risk reduction in the occurrence of morbidity and mortality events versus placebo¹</td>
<td>45%*</td>
</tr>
<tr>
<td>All-cause hospitalizations²</td>
<td>Risk reduced by 32%* and rate reduced by 33%*</td>
</tr>
<tr>
<td>PAH-related hospitalizations²</td>
<td>Risk reduced by 52%* and rate reduced by 50%*</td>
</tr>
</tbody>
</table>

SERAPHIN Trial of Macitentan
Primary endpoint: Morbidity and Mortality Events

Mechanisms of meds working on NO-cGMP Pathway
# NO-cGMP Pathway Agents

<table>
<thead>
<tr>
<th></th>
<th>Sildenafil</th>
<th>Tadalafil</th>
<th>Riociguat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td>PDE-5 inhibitor</td>
<td>PDE-5 inhibitor</td>
<td>Soluble guanylate cyclase stimulator</td>
</tr>
<tr>
<td><strong>Indication / FC</strong></td>
<td>II, III, IV</td>
<td>II, III, IV</td>
<td>II, III, IV</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Oral, IV</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>20 mg oral three times daily</td>
<td>40 mg daily</td>
<td>1 mg – 2.5 mg three times daily</td>
</tr>
</tbody>
</table>

## Riociguat for PAH

<table>
<thead>
<tr>
<th>Clinical Study</th>
<th>Doses</th>
<th>n</th>
<th>Study Duration</th>
<th>Study Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATENT RCT</td>
<td>1 mg, 1.5 mg, 2 mg, or 2.5 mg three times daily</td>
<td>443</td>
<td>12 weeks</td>
<td>Improvements in 6-MWD (36 m), PVR, NT-proBNP, FC, Dyspnea score, QOL measures, TTCW</td>
</tr>
</tbody>
</table>

**CHEST trial for Chronic Thromboembolic PH (CTEPH) — similar findings**  
**Riociguat only drug approved for Group 4 PH**

Riociguat for failing PDE5i Rx in PAH: RESPITE Clinical Trial

Study design
• Open-label
• N = 60 patients with poor response to a PDE-5i
• Study duration = 24 weeks
• Study endpoints
  – 6-MWD, cardiac index, NT-proBNP, functional class, quality of life, TTCW
• Study is ongoing

www.clinicaltrials.gov/ct2/show/NCT02007629

What about our case?

• What would be optimal PH therapy?
  Started with SQ treprostinil.
What about our case?

• Dyspnea better
• 6MWD back to 580 m NYHA Class II
• Intolerable discomfort due to site pain
• What to do now?

• Switch to oral treprostinil (Orenitram)
• Very aggressive uptitration to 10.5 mg tid
• Gradual worsening and after 3 mos represented with rt heart failure
• Placed back on IV treprostinil – added ambrisentan

Options for Patients Failing to Respond to First-Line Therapy

Functional Class III or IV (Treatment goals not met)

Combination Therapy (40%)
- Prostanoids
- Endothelin Receptor Antagonists
- PDE5 Inhibitors

Atrial septostomy and/or
Lung transplantation

Combination Therapy Trials

“Add-on” Trials

• PACES – sildenafil 80 tid added to stable eposprostenol. 26m ↑ 6MWD, slowing of clinical worsening
  – Simonneau et al AIM 2008
• STEP – inhaled iloprost added to bosentan. 26m ↑ 6MWD (p = 0.058), improved NYHA, slowed clinical worsening
  – McLaughlin et al, AJRCCM 2006

Upfront Combination Therapy: AMBITION Clinical Trial

Study design

• RCT
• n = 500 treatment-naïve Study groups
  – Ambrisentan
  – Tadalafil
  – Ambrisentan + tadalafil
• Study duration = event driven
• Primary endpoint = TTCW

Study results

• Combination therapy reduced the risk of clinical failure events by 50%
• SS* improvements in:
  – 6-MWD (50 v 25m)
  – NT-proBNP
  – % Patients with a satisfactory clinical response (39 v 29%)

Galie N et al. NEJM 2015:373:834-44.
**Events in AMBITION Trial**


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**Upfront Triple Combination Therapy**

**Study design**
- Retrospective review
- N = 18 treatment-naïve patients in FC III or IV
- Epoprostenol + bosentan + sildenafil
- First assessment of endpoints at 4 months

**Study results**
- SS* improvements in
  - 6-MWD
  - Hemodynamics
- Functional class
  - Improvement to FC I or II for 17 patients
- Overall patient survival
  - 100% at 1, 2, and 3 years

New Therapeutic Approaches

• Tyrosine kinases (imatinib)
• Small molecules (microRNA, CPPs)
• Bone morphogenic protein pathway
• Other novel agents
  – Bordoxolone – agent with anti-oxidant, antiproliferative, pro-apoptotic activity
  – Apoptosis signal-regulating kinase 1 (ASK1) inhibitor trial – MAPK and P38 inh

Summary

• Earlier detection, accurate classification and assessment of severity are important
• RV impairment in PAH must be met with aggressive action towards reversal
• An evidence-based treatment algorithm provides a foundation for disease management.
• Upfront combination therapy may become the standard of care for patients.
• Treatment is suboptimal – we need to discover and evaluate new therapies in well designed clinical trials